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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,626	11/26/2003	Daniel Pratt	19043-501	9707

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
09/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,626	PRATT ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-31 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-31 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 22-31 and 39-41 are pending. Applicants previously cancelled claim 3. Applicants have newly cancelled claims 1-2, 3-21, and 32-38. Upon discovery of new relevant prior art the previous statement concerning allowable subject matter is withdrawn and new rejections under 35 USC §103(a) are set forth below. Receipt and consideration of Applicants' amended claim set and remarks/arguments submitted on July 2, 2008 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-30 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. (U.S. Patent No. 5,560,933) ("Soon-Shiong").

Applicant Claims

Applicants claim (1) a method of administering a therapeutic agent within the central nervous system (CNS) comprising intrathecal administration of a composition to a subject's CNS, wherein said composition comprises a biodegradable polymer having a therapeutic agent and a buoyancy agent contained therein, wherein the buoyancy agent is selected from gases and oils and is controllably buoyant within the CSF.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Soon-Shiong teaches methods for in-vivo delivery (e.g. intrathecal administration) of substantially water insoluble pharmacologically active agents (e.g. taxol) and compositions useful thereof (title; abstract; col. 3, lines 24-29; and col. 4, lines 28-33). Soon-Shiong's invented compositions comprise particles of substantially water insoluble active agents contained

within a shell having a cross-sectional diameter of no greater than 10 microns, wherein a cross-sectional diameter of less than 1 micron is most preferred (col. 5, lines 23-30). Suitable active agents for incorporation into Soon-Shiong's invented compositions include **aspirin, ibuprofen, estrogen (i.e. a hormone), prednisolone, cortisone, hydrocortisone, anesthetics, immunosuppressive agents**, and preferably **taxol (i.e. a cytotoxic agent)** (col. 5, lines 31-56). The invented composition may also contain nutritional agents within the shell, such as **amino acids**, sugars, **proteins, carbohydrates**, **fat-soluble vitamins, such as vitamins A,D, E, and K**, and combinations thereof (col. 5, line 65 through col. 6, line 3). **Amino acids, sugars, proteins, carbohydrates, and vitamins A, E, and K read on active agents that are "other plant products".** The shell of Soon-Shiong's invented particles can be made of any natural or synthetic biocompatible polymer that may be cross-linked via the formation of disulfide linkages, such as **proteins** (e.g. **albumin, insulin, hemoglobin, immunoglobulins, fibronectin, fibrinogen,** etc.), **oligopeptides, polysaccharides** (e.g. starch, cellulose, chitin, dextrans, etc.), and synthetic polymers, which are amenable to chemical functionalization to introduce sulfhydryl moieties, such as polyvinyl alcohol, **polyhydroxyethyl methacrylate**, polyacrylic acid, polyacrylamide, polyvinyl pyrrolidone, etc.

Soon-Shiong teaches that optionally in the preparation of the compositions dispersing agents in which the active agent is dissolved or suspended may also be included, such as **vegetable oils (e.g. soybean oil, coconut oil, olive oil safflower oil, cotton seed oil, and the like**), aliphatic, cycloaliphatic, or aromatic hydrocarbons having 4-30 carbon atoms, aliphatic or aromatic alcohols, esters, ethers, and alkyl or aryl halides, all having 2-30 carbon atoms are indicated as being suitable dispersing agents (col. 6, lines 47 through col. 7, line 4). The

invented particles with a biocompatible shell and an active agent contained therein are typically **delivered as a suspension in a biocompatible aqueous liquid** (col. 7, lines 15-22). In the preparation of Soon-Shiong's invented compositions, it is contemplated that **the particle shells contain therein both the substantially water insoluble active agent dissolved or suspended in the dispersing agent** (col. 8, line 65 through col. 9, line 7). In Example 2 (col. 11, lines 12-35), Soon-Shiong teaches **an albumin protein shell containing soybean oil**. Shells comprising **a mixture of albumin and PEG-thiol** with a molecular weight of 2,000 g/mol are also exemplified in Example 11, col. 16, lines 20-55). The inclusion of PEG is art-recognized as increasing protein/enzyme in vivo circulation time and is expected to prolong drug release in vivo (col. 9, lines 38)

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Soon-Shiong does not exemplify a method of administering a therapeutic agent by intrathecal administration. This method, however, is suggested per the teachings of Soon-Shiong. Soon-Shiong does not explicitly teach the inclusion of buoyancy agents. This deficiency is nonetheless obvious per Soon-Shiong's teachings.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to utilize the invented particles to administer an active pharmaceutical agent intrathecally, because Soon-Shiong explicitly teaches that the invented compositions are suitable for the in vivo

administration of active substances and defines in vivo delivery to include intrathecal administration. Soon-Shiong does not explicitly teach the inclusion of buoyancy agents, however, Soon-Shiong's invented particles may comprise a dispersing agent, such as vegetable oils, which Applicants' admit are suitable buoyancy agents. Thus, Soon-Shiong's teachings suggest the administration of biocompatible aqueous suspensions of particles comprising (i) a biocompatible shell, such as cross-linked albumin, which is also biodegradable, and (ii) a substantially water insoluble active agent dissolved or suspended in a dispersing agent, such as soybean oil, which is necessarily a buoyancy agent, as admitted by Applicants. An ordinary skilled artisan would have been motivated to administer Soon-Shiong's compositions intrathecally and would have had a reasonable expectation of success in intrathecally administering these compositions, because Soon-Shiong's compositions are taught as being suitable for intrathecal administration. Regarding the intrathecal administration of Soon-Shiong's compositions to patients diagnosed with a central nervous system disorder, the preferred active agent in Soon-Shiong's compositions is a taxol, which is a well-known anticancer agent. Cancer reads on a central nervous system disorder, as evidenced by Applicants' claim 28. Regarding the incorporation of PEG (polyethylene glycol), it would have been prima facie obvious to include PEG. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments with respect to claims 22-30 and 40-41 have been considered but are moot in view of the new ground(s) of rejection.

Claims 31 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. (U.S. Patent No. 5,560,933) ("Soon-Shiong") as applied to claims 22-30 and 40-41 above, and further in view of Russell et al. (*Bone Marrow Transplantation*, 1999, *24*, pp 1177-1183) (already of record) and Vook et al. (US 2003/0129233).

Applicant Claims

Applicants claim method as described above, wherein the biodegradable polymer is poly(lactide-co-glycolide) (PLGA) and in some embodiments the active agent consists of living cells selected from bone marrow cells (e.g. red blood cells), fetal neural cells, or stem cells.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Soon-Shiong have been set forth above in the instant office action and are herein incorporated by reference. The teachings of Russell were set forth in the office action mailed 6/2/06 and are restated herein. Russell is provided herein to demonstrate that living cells, specifically bone marrow stem cells and blood cell stem cells, are art recognized therapeutic agents used in the treatment of leukemia. Leukemia is a kind of cancer and living cells are clearly substantially water insoluble active agents.

Russell teaches comparative studies of the treatment of patients with acute myelogenous leukemia (AML) and Myelodysplasia (MDS) who received sibling transplants **with stem cells** from peripheral blood (blood cell transplant, BCT) or bone marrow (BMT). Russell concluded by stating that while disease-free survival may be better using BCT than BMT for AML, it may greatly impair quality of life, due to a higher proportion of acute graft-versus-host disease (GVHD) (abstract).

Vook teaches particularly effective compositions for the localized delivery of chemotherapeutic hydrophobic anticancer agents, inclusive of **paclitaxel (taxol)**, doxorubicin, 5-fluorouracil, campthothecin, cisplatin, and metronidazole, their corresponding derivatives and functionally equivalents, and combinations thereof from **PLGA microspheres** [0006]. Vook's invented PLGA/Taxol microspheres afford controlled/sustained release of taxol and offer many clinical advantages, such as (1) improved patient compliance, as the number of drug dosings are decreased because the depot contains an amount of drug equivalent to multiple doses; (2) isolation depot from the tissue via its incorporation in PLGA thus reducing the drug concentration exposed to the one time and decreasing the chance of tissue injury of the drug copolymer, tissue at any at the depot site; (3) controlled drug release, which may allow for increased dosages of hydrophobic drugs to be administered without systemic toxicity complications. In terms of specific clinical applications of this technology, hydrophobic drug/PLGA formulations are envisioned to play a role in the treatment regiment of cancer and of infection [0287].

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Soon-Shiong lacks the teaching of an intrathecal administration method, wherein the active agent consists of living cells. This deficiency is cured by the teachings of Russell. Soon-Shiong lacks the teaching of an intrathecal administration method, wherein the biodegradable polymer is PLGA. This deficiency is cured by the teachings of Vook.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Soon-Shiong to substitute taxol for bone marrow stem cells or red blood stem cells, because both bone marrow stem cells or red blood stem cells have been shown as being suitable for treating leukemia a kind of cancer and taxol is a known anti-cancer agent. Furthermore, it would have been prima facie obvious to substitute taxol for bone marrow stem cells or red blood stem cells to treat leukemia, a kind of cancer, because both taxol and bone marrow stem cells or red blood stem cells are known to be suitable for the treatment of cancer. An ordinary skilled artisan would have been motivated to utilize bone marrow stem cells or red blood stem cells as the active agent in Soon-Shiong's invented compositions, because bone marrow stem cells or red blood stem cells are clearly substantially water insoluble active agents. An ordinary skilled artisan would have had a reasonable expectation of success upon incorporation of bone marrow stem cells or red blood stem cells into Soon-Shiong's invented compositions, because bone marrow stem cells or red blood stem cells are substantially water insoluble active agents. Regarding the use of PLGA as the biodegradable polymer shell, this would have been prima facie obvious, because PLGA is a

well-known conventional biocompatible and biodegradable polymer. An ordinary skilled artisan would have been motivated to modify Soon-Shiong's teachings and utilize PLGA/taxol microspheres, because PLGA/taxol microspheres are conventional compositions used to deliver taxol, are reasonable expected to enhance patient compliance due to the controlled/sustained release properties of the PLGA/taxol microspheres, and taxol is isolated from the body in the PLGA microsphere and, thus, less likely to induce tissue damage. An ordinary skilled artisan would have had a reasonable expectation of modifying Soon-Shiong's teachings to utilize PLGA as the polymer shell and obtain suspensions wherein the polymer shells contained taxol suspended in a dispersing agent (e.g. vegetable oil) and deliver the resulting composition intrathecally, because Soon-Shiong's compositions are suitable for intrathecal administration and taxol/PLGA are well known compositions. Thus, an ordinary skilled artisan would have been motivated to utilize Soon-Shiong's invented composition modified to contain bone marrow or red blood stem cells in to treat cancer via intrathecal administration with a reasonable expectation of success.

Response to Arguments

Applicant's arguments with respect to claims 31 and 39 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Claims 22-31 and 39-41 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571)

272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/James H Alstrum-Acevedo/
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